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	Patents ADP number *(if you know it)*	5451003
	If the applicant is a corporate body, give the country/state of its incorporation	UNITED KINGDOM
4.	Title of the invention	IMPLANTS FOR ADMINISTERING SUBSTANCES AND METHODS OF PRODUCING IMPLANTS
5.	Name of your agent *(if you have one)*	BARKER, BRETTELL & DUNCAN
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	138 HAGLEY ROAD EDGBASTON BIRMINGHAM B16 9PW Barker Brettell 138 Hagley Road Edgbaston BIRMINGHAM B16 9PW
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6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing *(day/month/year)*
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing *(day/month/year)*
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IMPLANTS FOR ADMINISTERING SUBSTANCES AND METHODS OF PRODUCING IMPLANTS

This invention relates to implants for administering substances. One embodiment of the invention is especially, but not exclusively, applicable to implants for administering micronutrient, or trace elements or minerals.

Drugs are most often currently administered orally by the ingestion of tablets, capsules or aerosols, or via subcutaneous, intramuscular or intravenous injections or implants. Oral solid dosage forms account for 40-50% of the market, parenteral products - 33% and the other more "novel" dosage forms (NDF's), only a few %. There is nonetheless enormous perceived potential for NDF's that can enhance a drug's therapeutic ratio and avoid patient non-compliance. Non-compliance remains a major issue despite 95% of patients being aware of its consequences. Common examples are incomplete courses of antibiotic therapy, using antidepressive drugs for too short a period, and forgetting to take contraceptive pills.

There are known implants that are implanted subcutaneously and which deliver a drug over a period of time in a controlled manner. These are typically based on polymer material systems. There are two basic types of implant for controlled drug delivery; “reservoir” and “monolithic” structures. “Reservoir” devices have layers which are corroded or absorbed by the body to release a depot of drug beneath these control layers. By having successive alternate control layers and drug layers the drug can be released over a period of time. “Monolithic” devices have the drug distributed throughout, so that release kinetics are controlled by slow corrosion and diffusion processes.

Problems include the so-called "burst effect" wherein an unwanted high fraction of the drug is released from the polymer capsule's internal surface quite soon upon in-vivo exposure. Another problem is the continuing need for high-purity, cost effective hosts that are capable of sustained drug delivery over months or years (for some applications).

Other known implants include inert ceramic implants which have the drug held in their pores, the drug having to leave the ceramic implant via a tortuous path of micropores, which delays its release and allows it to be controlled.

This invention concerns slow-release tissue-compatible implants, particularly suited to delivering low payloads of a therapeutic substance to a specific site and/or over a long period of time ("long" may be months or years). Although delivered to the site of the implant the beneficial substance may be taken up by the body globally, and may have an effect at another site. In the past the major limiting factor for most drug delivery systems that use implanted materials (polymers or ceramics) has been the "payload" achievable. With the advent of new genetically engineered, more potent drugs (peptides, proteins, DNA fragments), miniaturised delivery systems are becoming more and more attractive, provided designs ensure patient safety. An example of such a safety issue for in-vivo administration would be the failure of an electronic "gate" linked to a large on-chip liquid reservoir. Such concerns can be addressed by the use of drug delivery arrays or drug incorporation within a resorbable host material.

According to a first aspect the invention comprises a silicon implant provided with a substance to be administered to the implanted subject.

Preferably the implant comprises porous silicon. The porous silicon may have a porosity of at least 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or higher (the porosity is the fractional void content by volume). The porous silicon may have a porosity that is in a range between any two of the figures mentioned above.

The implant may have a coating, region, or layer of silicon, or it may be silicon substantially throughout its cross-section. The implant may have a layer of material over the silicon, for example a coating of hydroxyapatite. The over-layer of material may have a physiological effect upon implanting of the implant.

The silicon may be polycrystalline silicon.

Said substance may be distributed in the solid phase silicon material substantially uniformly. In the case of porous silicon said substance may be distributed in the pore network and/or in the silicon skeleton. It is envisaged that distributing the substance in the material of the skeleton may give greater control over the release rate of the substance since this will be related directly to the erosion rate of the silicon material. With a substance held in pores the release rate is also dependent upon how quickly the material can escape the pores (before the skeleton has eroded). This may or may not be desirable or acceptable. In the case of polycrystalline silicon the substance could be distributed in the grains and/or grain boundaries.

It has been appreciated that silicon, and in particular porous silicon, has very good properties which enable it to serve as a drug or micronutrient delivery vehicle. Experimental evidence in support of the suitability of porous silicon as a substance delivery vehicle in an implant has been obtained. Studies by the inventors have shown that porous silicon is "resorbable" or "bio-erodible", and is resorbed or eroded by the mammalian body at a slow enough rate to make long-term porous silicon implants a practical way to deliver drugs/substances.

Highly porous silicon has long been known to be unstable structurally and chemically, and researchers in the opto-electronics field have gone to great lengths to make it more stable for opto-electronic applications. It is ironic that the lack of stability/inert properties of porous silicon now, with hindsight, is a factor in the controlled delivery of substances by implants.

Tests show that high porosity (e.g. 80%) silicon is resorbed faster than medium porosity (e.g. 50%) silicon, which is in turn resorbed faster than bulk silicon (which shows little, if any, signs of being resorbed). Thus, by adjusting the pore size and total volume of pore to skeleton in porous silicon it is possible to tune the silicon material to be resorbed faster or slower.

Microporous silicon (pore size less than 2 nm), mesoporous silicon (pore size 2-50 nm) and macroporous silicon (pore size >50 nm) are all suitable carrier materials for erosion.

Silicon is cheap, and is available in very pure forms (e.g. the electronics industry already has a requirement for clean, pure, silicon

wafers). Moreover, it is already known how to dope silicon crystals with a very wide range of elements, albeit in a different field and albeit at very low concentrations (lower concentrations than required for micronutrients).

It is envisaged that having a beneficial substance provided in porous silicon implant as a delivery mechanism will be especially appropriate for delivering substances which do not need to be delivered at high doses. It is envisaged that a porous silicon implant may be about 0.5 x 0.5 x 4 mm in size (or in the ranges >0 to 2 mm x >0 to 20 mm x >0 to 20 mm). Each implant may have a weight of less than a milligramme, or a few milligrammes, or a few tens or hundreds of milligrammes, and each tablet may conveniently be doped with a "dry payload" of tens to hundreds of microgrammes of substance, or even to a few milligrammes (or more if it is possible to carry it). This may be insufficient for delivery of macronutrients, or macro dose drugs, but it is sufficient to deliver substances which are needed in the micro to milligramme range.

One area where porous silicon is suitable as a carrier for a therapeutic or beneficial substance is in the provision of micronutrients or microminerals to subjects.

Some trace minerals needed by the body are present at extremely low concentration in the body (e.g. selenium, chromium, manganese and molybdenum). The recommended daily allowance (RDA) of microminerals can be <0.1 mg/day and yet deficiency effects are well documented (e.g. selenium iodine). This is often because only a small and highly variable fraction of orally-ingested microminerals are absorbed and hence become bio-available. Having these microminerals delivered

by an implanted silicon tablet that is fully adsorbed is an attractive solution to deficiency problems. Moreover, by having the substances in an implant it is possible to deliver a substance to a specific site (e.g. iodine to or near the thyroid gland).

Silicon itself is an essential trace element, and a porous silicon implant could, of course, be used to deliver silicon in which case it may not carry any other beneficial substance.

The implant may have more than one beneficial substance. A multi-essential trace element implant having 2, 3, 4, 5 or more trace elements may be provided.

Other elements have widespread use clinically for therapeutic purposes, e.g. lithium for depression, gold and silver for antibacterial properties, and platinum for neoplastic diseases. These may be administered not so much to achieve a desirable "normal" mineral content in the physiology of a subject, but to increase levels of microminerals to therapeutic levels, possibly at a specific locality. The dose levels of such therapeutic elements in the blood stream are normally in the μg/l range, which is within the capabilities of porous silicon implants.

A therapeutic or essential trace element (or other element) may be delivered in non-elemental form. For example, a salt of a metal may be the beneficial substance, metal ions being available to the body of the patient. So long as the substance is delivered in a physiologically usable form, how it is carried in the erodable material (compounded or elemental) may not matter.

It will be appreciated that implanting an implant which can deliver a controlled amount of a drug/micronutrient/micromineral for a month, or even two or three months, or a year, or possibly even years, has great advantages over relying on a patient to eat correctly or take oral tablets correctly, especially when the disorder being treated exacerbates any difficulties in the patient having a discipline to take the remedy. The fact that a silicon implant can be made to break down slowly makes it possible to leave an implant alone for a long time. When a sustained level of drug dose delivery is required a silicon implant can be engineered to deliver a prolonged sustained substantially constant (or constant enough for the intended purpose) level of drug or mineral. Using implants to deliver trace elements is attractive for those people who have gastrointestinal tract disorders and who cannot absorb some elements orally. Even if a patient were to be treatable orally there can be a great variation in the level of absorption achieved in people's guts and the same level of oral dietary supplement may result in different levels of absorbed mineral. Subcutaneous absorption has significantly less variation between people and is therefore more easily controlled.

A feature of virtually all drugs, especially large organic molecules, however is that they cannot survive high temperatures. If a silicon implant is made using high temperature doping techniques it may not be possible to get the structural silicon material of the implant to take up some molecules in a functional state. However, this is not a problem for therapeutic elements (e.g. Li, Se, etc.).

Of course, it is possible to use techniques other than thermal drive in to get drugs into the depths of an implant and/or into the solid phase of the porous skeleton. We could use vacuum evaporation, or build the implant up in layers, with the substance adhering predominantly to the

surface of each layer, or indeed any suitable technique for distributing the substance throughout the body of the erodable implant.

The geometric design of known monolithic drug release implants can be used to control the drug release rate, and similar techniques of geometric design can be used to control substance release from silicon implants. This may be in addition to controlling the porosity, and pore size of porous silicon to control the rate of dissolution of the implant. The implant may have different porosity at different depths.

Of course, the silicon implant need not necessarily have its erodable carrier material of pure silicon, or substantially pure silicon. Now that it has been established that silicon works it is predictable that silicon carbide and silicon nitride may also have similar properties. Indeed, as a generalisation, a silicon-based compound which has the corrosion properties desired (corroding at a generally constant rate over months or years) and which is non-toxic at the levels released, and which otherwise has no unacceptable harmful effects, would be suitable in place of pure (or substantially pure) silicon as the carrier material, but silicon is still currently preferred.

According to a second aspect the invention comprises a porous or polycrystalline implant provided with a substance to be administered to the implanted subject, the implant being made substantially of an element.

Preferably the implant is made of porous or polycrystalline semiconductor.

Although tests by the inventors in vivo show that porous silicon is corroded if subcutaneously implanted, the inventors also have in vitro

tests using simulated body fluid (SBF) which shows that porous and polycrystalline silicon behave in a similar way in SBF.

The realisation that silicon, and especially porous silicon and/or polycrystalline silicon, are suitable materials to be bio-eroded by the body in a controlled manner, and the realisation that this can be used to release drugs/substances into the body (or to a localised area), can be further expanded. The implant may have a plurality of drug payload areas defined in a body of silicon, the body of silicon having a plurality of barrier regions, or doors, adapted to be resorbed in use by the body, the geometry and size of the barrier regions being such that in use at least a first barrier region is eroded or resorbed such that the drug payload in the drug payload area adjacent said first barrier region is released to the body before a second barrier region, adjacent a second drug payload area, is resorbed sufficiently to enable the second drug payload to be released, thereby providing a time-differential breakdown of at least the first and second barrier areas and hence a sequential release of said first and second drug payloads.

The first and second drug payloads may comprise the same drug, or different drugs.

There may be three or more barrier regions each adapted to be corroded at different times, and adapted to release drug payloads from respective drug payload areas at different times.

The barrier regions may comprise porous silicon, such as mesoporous silicon or microporous silicon. The barrier regions may comprise polycrystalline silicon. The rate of erosion of the silicon can be controlled by controlling the porosity (higher porosity materials are

corroded faster) and the pore size (smaller pores for same porosity are corroded faster), and the barrier thickness.

Instead of having one implant with a plurality of drug payloads it may be desirable to provide a plurality of separate implants with drug payloads and barrier regions adapted to release the drug payloads at different times.

The implant may comprise a tablet. The tablet may comprise an array of drug payload reservoirs each containing a respective drug payload. The tablet may have a longitudinal direction and the respective barrier regions associated with respective drug payloads may be spaced apart in the longitudinal direction. The implant may be adapted to be corroded in a direction transverse to the longitudinal direction, and preferably at right angles to it, in order to release the respective drug payloads. The implant may have a longitudinally extending surface portion and the drug payload areas may be separated from the surface portion by barrier regions requiring different times of attack by body fluids to be corroded. The different corrosion times of the different barrier regions could be afforded by different thicknesses of barrier region. Alternatively, or additionally, the silicon material of the implant may have different corrosion properties at different barrier regions (e.g. they could be made of porous silicon of different porosity).

Embodiments of the invention will now be described by way of example only, with reference to the accompanying drawings, in which:-

Figures 1A to 1D show scanning electronic micrographs at x3000 magnification of a titanium implant explanted from a guinea pig at 0, 1, 4, and 12 weeks after implant, respectively;

Figures 2A to 2D show scanning electronic micrographs at x3000 magnification of a porous silicon implant explanted from a guinea pig at 0, 1, 4 and 12 weeks after implant respectively;

Figures 3A to 3D show scanning electron micrographs at x3000 magnification of a porous silicon implant partially coated with hydroxyapatite (HA) and explanted from a guinea pig at 0, 1, 4, and 12 weeks after implant respectively;

Figure 4A shows schematically a silicon wafer micromachined to form thousands of implants;

Figures 4B and 4C show two implant structures;

Figure 5 shows a table of elements which may be administered using the present invention, those elements being indicated by the key as being essential trace elements, and/or having deficiency problems are those which are preferably incorporated in an implant;

Figure 6 shows another embodiment of the invention in which there are a plurality of drug payloads provided on a resorbable tablet; and

Figures 7 to 9 show alternative multi-drug tablet implants.

Figures 1A to 1D show that over a 12-week period of tests a titanium implant subcutaneously implanted in a guinea pig exhibits little change to its surface - it is bioinert.

Figures 2A to 2D show that when a porous silicon subcutaneous implant (30% porosity) is examined at 0, 1, 4 and 12 weeks there are substantial changes to the porous surface of the implant. There is considerable corrosion of the porous silicon, even to the extent that the layer of porous silicon above the bulk silicon body (upon which the porous silicon is formed) was totally eroded at places.

The discs used in the in-vivo trials were made as follows:

(a) Titanium Discs

Titanium foil of 99.6+% purity was purchased from Goodfellow Metals Limited in the form of punched-out discs of 0.5 mm thickness and diameter 11.5 mm. These were subsequently abraded (on both faces) with 12 μm diamond powder to remove any burrs introduced by the punch-out process and to develop equal degrees of surface roughness on both faces. Batches of 10 discs were then chemically etched at a time after cleaning in an ultrasonically agitated acetone bath for 20 minutes. The discs were isotropically etched (to remove surface damage) for 2 minutes in a stirred solution of 35 ml H_2O, 10 ml HNO_3 and 5 ml 40% HF. The etch process was quenched with DI water and discs were thoroughly rinsed in DI water prior to drying on filter paper.

(b) Bulk Silicon Discs

Batches of 12 mm wide discs were sawn out of ~5" (100 mm) diameter CZ wafers (N^+, phosphorous-doped 0.0104.0.0156Ωcm resistivity, 0.5 mm thick, (100) orientation) using a custom-built drill bit. Discs were cleaned in "meths", then ethyl acetate and then in an

ultrasonically agitated acetone bath. Smoothing of the disc edges, removal of saw damage and equality of surface roughness on both faces was achieved using a "polish etch": 25 ml HNO_3 + 5 ml HF (40%) + 5 ml acetic acid. Batches of 10 discs at a time were given a 5-minute etch with continuous stirring followed by a DI H_2O quench and rinse with drying on filter paper.

(c) Porous Silicon Discs

The chemically polished bulk Si discs were anodised sequentially, one at a time, in a custom-built electrolytic cell that enabled both faces and edges to be porosified. Discs were held at one edge by a platinum "croc-clip" and lowered and raised in a controlled manner by a stepping motor into electrolyte in a cylindrical Pt crucible that formed the cathode. Each disc was anodised potentiostatically (i.e. at a constant voltage of 1.0 V) in 40% aqueous HF for a period of 10 minutes. With this type of arrangement most current flow occurs via the meniscus, so the procedure adopted was to slowly raise the meniscus up to the centre of the disc, remove the half-anodised disc, dry it and then invert it, to anodise its other half in the same manner. Fully anodised discs were by this process completely covered in an ~30μm thick coating of porous silicon. They were rinsed in DI H_2O and dried on filter paper.

(d) Sterilisation

All discs were stored in air prior to sterilisation by "autoclaving" at 134°C for 10 minutes in pressurised steam.

Figures 3A to 3D show similar corrosion/resorbtion of coated porous silicon, 30% porosity, (coated with hydyroxapatite). The rate of

corrosion appears to be slower for the coated porous silicon. Coating the silicon with other materials may delay, or speed up corrosion at early stages, depending upon the coating material used. This can be used to give a high initial dose of substance and then a lower dose (possibly for a prolonged time), or a low initial dose (or no dose) initially, followed by a higher dose later.

Figures 2 and 3 show that the corrosion of porous silicon in mammals does take place, and in a progressive manner.

Tests were also done to ensure that the silicon implants did not cause any serious problems to the guinea pigs, and again these tests show that using silicon, and especially porous silicon, as a biologically acceptable material is viable in a subcutaneous site. The pathological test results are given in Appendix 1 which forms part of this patent application.

The 12-week tests described above have been followed by a 26-week study which has shown entirely consistent results: there is a steady corrosion of porous silicon, and the corrosion of the implants did not cause any significant harmful effects on the test subjects. There was no gross inflammatory response, no significant fibrotic scarring, and excreting the corroded silicon was not a problem.

Since the corrosion of polymer is known and tested as a delivery mechanism for drugs, the present invention is, with the support of the tests discussed, fully realisable. Nevertheless the concept of using semiconductor tablets for prolonged in-vivo drug delivery is completely novel.

Figure 4 shows a silicon disc 40 machined to produce many thousands of implant tablets 42. It is envisaged that hundreds or thousands of tablets could be made from an 8 inch (200 mm) diameter wafer.

The wafer is treated so as to cause it to become porous throughout its depth, and then broken into discrete tablets. The tablets are then smoothed to facilitate subcutaneous insertion and acceptability. An elongate tablet, such as that shown, may be suitable for injection through a needle. The rounded ends 44 of the elongate tablet may help this. The tablets may take the form of that shown in Figure 4B.

In an alternative arrangement shown in Figure 4C a disc 46 of about 20-25 mm diameter is shown. This is surgically subcutaneously implanted.

It will be appreciated that the implants 42 and 46 are completely eroded in the body and do not need surgically removing.

Figure 5 shows elements considered suitable for incorporation into silicon implants which rely upon the corrosion/resorbtion of the silicon material to deliver an active substance (the element). It is envisaged that implants will be provided having one or more of the elements indicated as being essential trace elements, and most preferably those indicated as being essential trace elements with deficiency problems.

It is also, of course, envisaged to administer therapeutic elements or substances for particular disorders.

Furthermore, in the case of a problem associated with an excess of an element, or excess of a substance, the implant could be used to administer a blocker to prevent the excess substance operating properly, or something to bind to or react with the excess substance, reducing the effective excess. For example, it has been proposed that silicon in the form of silicic acid can beneficially assist in aluminium excretion.

There is no theoretical reason why an element such as iron cannot be administered using the present invention, but it may as a practical matter be difficult to get a sufficiently high dose of Fe into a silicon tablet to make it sensible to implant an implant.

Elements which are preferred for incorporation into a silicon micromineral tablet include: Vn, Cr, Mn, Se, Mo (dietary requirements), Li, Ag, Au, Pt (therapeutic effect).

As well as silicon other suitable biocorrodable semiconductors to use as carriers for beneficial substances include germanium, silicon carbide and silicon nitride. The semiconductor material could be doped or undoped. Silicon carbide may have anti-thrombogeric properties, and silicon nitride may have orthopaedic applications.

There is no reason why molecules, as well as elements, cannot be delivered, so long as the technique for getting the drug/desirable substance into the implant does not destroy the efficiency of the substance, and so long as they are released in a form which is active when the silicon is broken down.

In the case of minerals/trace elements one way of producing micromineral tablets is:

(1). create porous silicon: for example by anodising a whole silicon wafer to introduce a low concentration of mesopores (e.g. 30% porosity) - this is done using HF acid and an electric potential in a known manner (see for example US Patent 5 348 618 which discusses creating porous silicon using HF acid to achieve partial electrochemical dissolution - the contents of US 5 348 618 are hereby incorporated by reference);

(2). use wafer dicing and wet-etching techniques that are standard in the silicon semiconductor industry (or any other techniques) to define smooth tablets (sharp edges are undesirable);

The order of (1) and (2) may be reversed.

(3). impregnate the tablets: for example by immersing them in an aqueous solution of the mineral, or minerals, to be impregnated (the tablets could contain more than one mineral) and then driving in the minerals using a thermal drive-in technique, for example put the saturated tablets in an oven at 800°C for thirty minutes;

(4). clean the tablets (if necessary).

Another way of getting a substance into the implant is to put a salt of a mineral on the surface, heat in an inert atmosphere (e.g. argon) until the material melts and wets the porous structure. The insert/wafer can then be cooled down, and any excess substance washed off in water. A thermal drive in operation can then be performed.

It is preferred to drive the mineral into the solid phase of the porous structure, rather than leave it solely in the pores. This gives greater control of the dissolution rate of the mineral and eliminates the "burst-effect" problem common with polymer-based systems.

A combination of a knowledge of the dissolution rate of the tablets, and how that behaves with time, and the doping level of the tablets, and how uniform that it, gives the ability to control the dosage of substance administered over time.

Figure 6 shows a schematic cross-section of a multi-reservoir silicon tablet 60 (not to scale). The tablet 60 comprises a first portion 62 joined, for example by medical adhesive (or by wafer bonding), to a second portion 64 at interface 65. In this example, the first and second portions are mirror images of each other, and are identical (they are symmetric). Each half 62 or 64 of the tablet has side peripheral, or rim, portions 66 and a top (or bottom) wall portion 68. Each half of the tablet has micromachined in it a large number of reservoirs 70 which, in the assembled finished tablet, contain drug material 72. The reservoirs are separated by island walls 74 of silicon. The tablet 60 (including the rim portions 66, top/bottom portion 68, and island walls 74) is made of resorbable porous silicon which is corroded and absorbed by the body when implanted. The fact that the two portions 62 and 64 are substantially identical makes it cheaper to manufacture them since there is only one shape to machine.

In the example shown in Figure 6, distance D4 is shortest and the wall thickness in the region D4 is breached first by corrosion of the porous silicon, releasing the contents of reservoir R1 first. Next reservoirs R2 and R3 are released as the next thinnest wall portions 76 in

those regions corrodes away and is breached. Then wall portions 78 corrode releasing the contents of reservoirs R4 and R5, and so on.

By having barrier walls of different thicknesses it is possible to achieve controlled - and sustained - drug release as reservoirs are sequentially opened.

The distances D1, D2 and D3 are such that the "lid" thickness D4 is significantly thinner than the rim thickness D2. Thus, the micromachining of the depths of the reservoirs controls the release time of the outer reservoir, rather than its proximity to the peripheral edge of the silicon wafer. Similarly, D3 is large enough between adjacent reservoirs that it is the "lid" thickness that is corroded first, and not the island walls 74 between adjacent reservoirs (after one reservoir has already been opened to body fluids corrosion of the island walls occurs).

Of course, we may prefer to have the progressive opening of reservoirs achieved by corrosion of the dividing walls between adjacent reservoirs, instead of or in addition to the corrosion of peripheral surfaces of the tablet.

It will be appreciated that the reservoirs of drug material could hold beneficial substance in any form, for example liquid drug, or powder drug, or solid drug. The drug could be a complex organic molecule, or it could be a micronutrient or micromineral as previously discussed.

The reservoirs of drugs could contain a micromineral tablet, or other tablet/implant. A reservoir hole may contain a plurality of erodable drug/element delivery tablets/implants, which may contain the same or different beneficial substances, and/or may be corroded at different/the

same rates. Thus, the doors to reservoirs may be separately eroded to allow physiological access to tablets which in turn release a beneficial substance in a controlled manner over days, weeks or months. There may be several tablets in a reservoir, or tens of tablets, or hundreds of tablets.

The "reservoirs" need not necessarily be machined holes in a body of resorbable porous silicon material, they could be regions which have been differentially impregnated with a beneficial substance in comparison with the "walls" (or they could be regions which otherwise have a differential level of beneficial material in comparison with the "wall" regions). Thus, the implant may be a solid body (possibly made from discrete sections, but with no actual holes). However, at present, it is envisaged that micromachining an array of holes will probably be best.

The wall regions can be considered to be time delay means adapted to delay the timing of release of the contents of the reservoirs.

It will be appreciated that silicon technology is indeed ideally suited to compartmentalising drug payloads - an attribute that is exploited in this invention. The basic idea is to micromachine an enormous number (e.g. 10^2-10^4) of independent reservoirs into resorbable blocks of Si, thereby generating a new way of controlling kinetics of drug release. The time of release from each reservoir is predetermined by the overlying thickness of a microporous "lid" that is gradually eroded in-vivo.

The example of Figure 6 may be created by anodising right through two Si wafers, then deep dry etching an array of photolithographically defined cavities in both, and finally bonding them together after reservoir filling. The kinetics of release are determined by the volume distribution and lid thickness distribution within the array. For this to be the case the

diffusion time of a high molecular weight drug (which may be a typical drug) through the "lid" is made infinitely long compared with its erosion rate. This is achieved via lid topography (use of micropores < 2 nm width) or pore surface chemistry (e.g. hydrophobicity with hydrophilic drugs). Alternatively the drug deposit is itself in solid form until the physiological fluids break through into the reservoir.

The arrangement of Figure 6 is one way of providing a multi-reservoir, time-differential release implant. Similar effects can be achieved by the implant 71 of Figure 7 which shows a lid 73 made of very slowly corroded material and a base 75 made of faster corroding material. A flat interface between the lid 71 and the base 73 may make it easier to assemble the implant. The depths referenced 77 control the release time of the reservoirs.

One of the reservoirs in Figure 7 is shown containing a number of micromineral porous silicon tablets 79. The lid 73 could, of course, be made of a material that corrodes at the same rate as the base (e.g. of the same material).

Figure 8 shows an arrangement and a flat lower surface 86. The profile of the lid matches the "doors" of the base so as to achieve breakthrough of the lid and base at regions adjacent any particular reservoir generally at the same time.

Figure 9 shows an implant 90 having a base and a lid 92. The base 91 has reservoirs 93 of generally the same depth, and barrier regions 94 of generally the same depth. The lid 92 has a stepped/profiled upper surface topography arranged to ensure sequential,

time-differentiated, breakthrough into the reservoirs (the lid is corroded through first, not the base).

The multi-reservoir implanted discussed are all fully resorbable, and do not require surgical removal, but the invention is also applicable to non-corrodable implants having corrodable doors. The non-corrodable part of the implant may be bulk silicon.

The above types of delivery system offer much better control and predictability of delivery rates than conventional "monolithic" polymer systems. In the latter case drug release rates are often determined by diffusion through a tortuous pore network, at least for sustained release.

It will also be appreciated that the technical effect achieved by the embodiment of Figures 6 to 9 can be achieved using other corrodable materials beyond silicon. Indeed, in one aspect the invention is not restricted to silicon material for the construction of a multi-reservoir progressive drug release implant. Any suitable material may be used.

According to another aspect the invention comprises an implant having a plurality of reservoirs, a plurality of beneficial substance charges provided on said reservoirs, and a plurality of barrier regions, or doors, provided adjacent said reservoirs, the doors having a plurality of different erosion times when implanted, the arrangement being such that in use the doors are broken down sequentially in order to stagger the release of the contents of the reservoirs.

There may be up to ten reservoirs, of the order of tens of reservoirs, or even of the order of hundreds of reservoirs, or more.

The invention also comprises a method of timing the release of beneficial substances in an implant.

The fact that silicon does not resorb too quickly is beneficial. It is preferred to have an implant that will not need replacing for at least one month, and most preferably for at least two months, three months, four months, six months, nine months, or a year or more.

A problem with using the erosion of an implant to deliver drug embedded in the material of the implant is that the surface area of the implant changes with time (or can change with time) and hence the drug delivery changes with time. For example, a sphere gets smaller. This can in part be countered by the geometric design of the implant to allow the creation of an expanding internal surface to compensate for a contracting external surface.

An alternative, or complementary, approach that is now realisable with porous silicon, and with polycrystalline silicon, is to ensure that the drug/beneficial substance is present at different concentrations at different regions of an implant. This can be achieved by controlling the pore size through the depth of a body of porous silicon, or by controlling the grain size/number of grain boundaries. The number and/or size of grain boundaries may be controlled throughout the depth of a body of polycrystalline silicon. Thus, it is possible to have a porous silicon tablet which has a substantially uniform dose delivery rate with time as it is resorbed due to the concentration of drug/micromineral in it increasing towards its centre so as to balance the decrease in exposed surface area.

It will be noted that substantially 2-dimensional shapes, such as a disc, do not suffer so much from changes in surface area, and neither do the elongate "line" shapes (as shown in Figures 4B and 4C).

In addition to the porosity affecting the amount of substance that can be held in microporous silicon (greater porosity, greater substance-containing capability), the pore size can affect the rate of dissolution of the implant. Thus, the inner regions of a porous silicon implant can be arranged to corrode faster than the outer regions, again having a compensating effect for the loss of exposed surface area.

Whilst many countries do not, yet, permit the patenting of methods of treatment of the human or animal body by surgery or therapy, there are some (e.g. USA) who do. In order for there to be no doubt about the Paris Convention priority entitlement to such an invention in those countries that do permit it, the invention also comprises the treatment, therapeutic or prophylactic, of a disorder of the human or animal body by implanting a silicon implant and allowing the implant to corrode or be resorbed so as to realise a beneficial substance which helps to alleviate or ameliorate the disorder, or to prevent the disorder from occurring. The implant will typically be implanted subcutaneously.

Furthermore, the technique could be used to release diagnostic substances, possibly in a localised region of the body. Diagnostic substances are “beneficial substances”.

It will be appreciated that the realisation that silicon structures, especially porous silicon and polycrystalline silicon structures are able to be broken down by the body over a long (months) period of time without evidence of significant harmful effects has led to the ability to create

beneficial substance (e.g. micronutrients and drug) delivery implants which take advantage of this. The evidence showing no detrimental effects of implantation enables us to have a reasonable and predictable expectation of success - it is more than speculation.

At present, it is perceived that restrictions on the physical size of the drug payload for implants will restrict their practical use to delivering microminerals, or other substances, which are not required at high levels (e.g. genetically engineered proteins, peptides, and gene fragments, and other DNA material). However, the invention is not necessarily to be restricted to those areas if a practical macro-drug delivery implant is created.

A "beneficial substance" is something beneficial overall: it could be a toxin toxic to undesirable cells/to interfere with an undesirable physiological process. For example, anti-cancer substances would be considered "beneficial", even though their aim is to kill cancer cells.

It will be noted that the terms "eroded", "corroded", "resorbed" are all used herein. The mechanism of corrosion is not fully known, but that erosion, corrosion takes place is proved. Bioerosion, bioresorption, biodegradation are other possible terms: at present whether the silicon/carrier material is taken up into cells or stays extracellular is not considered important. It is not intended, necessarily, for the invention to be restricted to any precise biological distinction between the "corrosion" terms used.

APPENDIX I

Invivo trial of Porous Silicons Implant

Purpose

The purpose of the trial was to evaluate the biocompatibility of porous silicon when implanted at subcutaneous sites in guinea pigs in order to investigate the materials' suitability for use in implantable devices.

Trial Protocol

Experiments were conducted in accordance with the methods specified in the International Standard for biological evaluation of medical devices part 6 (ISO 10993-6).

The test specimens were in the form of discs (10 mm in diameter, 0.3 mm in thickness). Manipulation of their surface characteristics aimed to make 1 specimen type bioactive (ie encourage tissue attachment; hereafter termed porous silicon), 1 bioinert (ie produce no interaction with living tissues; hereafter termed bulk silicon) and 1 specimen type bioactive pre-coated with hydroxyapatite (hereinafter termed coated porous silicon). One of each specimen type and one control (titanium disc of the same dimensions as the test specimens) were used per animal.

This trial used a total of 30 guinea pigs. The pilot phase of the trial took place over two weeks and used 3 guinea pigs. The pilot study was successful (ie no gross reactions to the implants occurred) so the full scale study proceeded as planned. The full study used a further 27 guinea pigs - 10 per time point examined (1, 4 and 12 weeks post-implant).

Animals were acclimatised to the Experimental Animal House (EAH) environment for at least 5 days prior to experimentation. Following this period each animal was implanted with a transponder (Biomedic Data Systems) for identification and to enable body temperature to be monitored throughout the procedure. The transponder was implanted subcutaneously via a 12 gauge needle in the dorsal region, at a site where it did not interfere with the subsequent implantation of silicon or control specimens. The area of injection was shaved and a local anaesthetic used.

4-7 days later animals were given a general anaesthetic (Halothane 1.5-2.5%) and 4 test specimens implanted. The back of the animal was shaved and an incision of the skin made. Subcutaneous pockets were made by blunt dissection, with the base of the pocket at least 15 mm from the line of the incision. One implant was placed in each pocket, and the implants were at least 5 mm from each other. Four pockets were made to allow placement of 4 implants. The incision was closed by use of appropriate suture material.

Following surgery body temperature (via the transponder) was taken two times per day for one week (pilot study) or up to 12 weeks (full study) following surgery and animals closely observed during temperature taking. Each of the implant sites was closely examined and the extent of any reaction noted. The diameter of each implant site was measured to assess swelling and any reddening scored (0 = normal, no different from surround skin; 1 = some light red coloration in patches; 2 = uniform light red coloration or patches of darker red; 3 = darker red over all of implant site). Animals were selected at intervals of 1 week (pilot

study) or 1, 4 and 12 weeks, and culled. The implant sites were carefully inspected and standard tissue sections of each site were submitted, stained with haematoxylin and eosin and evaluated for various pathological features using a Zeiss Axioplan Photomicroscope. A range of pathological features reflecting the tissue response including acute inflammation and fibrosis were graded by assigning a numerical score to each feature; by comparing score grades with respect to time and implant site, an objective comparison of the silicon materials was obtained. The criteria used in assigning score grades for each pathological feature assessed are summarised in Annex (A). The specimen type at each implant site was randomised and the experiments and evaluation conducted blind.

The scores or values for each specimen type and each time point were compared with those of the control specimens using appropriate non-parametric tests. Multi-factorial analysis of variance was used where possible, with ad hoc tests for differences between groups.

Mean temperature (figure 1) and weight (figure 2) data is shown in graphical form at Annex B. There was a significant rise in temperature (figure 3) and a significant decrease in weight gain (figure 4) for the 7 day period following surgery in all 3 groups of animals (1,4 and 12 weeks). Thereafter a steady decline in body temperature and a steady increase in weight was apparent, indicating that no chronic inflammatory reaction to the implants has occurred. The transient effects on temperature and weight gain are due to the surgical procedure and unrelated to the nature of the implants.

At the time of performing the histological appraisal, the allocation of test and control sites for each experimental animal was unknown and the histological examination was performed blind. Following appraisal, the results were decoded: a summary of the score grades for each implant type with respect to animal number, histological feature and time-point are summarised in the tables presented at Annexes C-E. In general the autopsy examination revealed no evidence of any significant pathological change at any of the three time-points. In particular, all implants were easily extracted from their respective implantation sites and showed no evidence of fibrotic tethering to the surrounding connective tissues. At the earliest time-point each site showed obvious acute inflammation associated with mild to moderate neo-vascularization. These changes were almost exclusively limited to the implantation site. The histological findings were entirely consistent with the features noted at autopsy. The scores for each of the four classes of pathology (Annexes C-E) were compared with respect to time (ie week 1 vs. week 4 vs. week 12) and implant type (the scores of each silicon type compared with the titanium control). Details of the statistical analysis are shown at Annex F.

Acute inflammation at week 1 was significantly greater than at weeks 4 and 12 but no difference was found between weeks 4 and 12 (table 1, Annex F). Tissue degeneration was significantly higher at weeks 1 and 4 when compared to week 12, with no difference between weeks 1 and 4. New vessel granulation tissue formation was significantly higher at week 1 than at week 4, which in turn was significantly higher than at week 12. Chronic inflammation was significantly higher at week 4 than at week 12, which was significantly higher than at week 1. In general, these significant findings were consistent with the three distinct patterns of pathological change observed at the three excision time-points, summarised in the following four paragraphs.

All sites at one week post-implantation showed features that reflected the immediate response to the injury induced by the surgical procedures to implant the materials. Most

sites showed moderate acute inflammation with infiltration of the tissues at the implantation site by neutrophils and macrophages. These changes were associated at the majority of sites with oedema of the connective tissues, focal haemorrhage and necrosis and early invasion of the margins of the implant site by proliferating capillary loops. At no site did these changes extend beyond the margins of the implant and into the surrounding skin above or skeletal muscle below.

Although a very few sites showed persistent, low grade acute inflammation four weeks post-implantation, the majority of sites showed features that were consistent with the progression of the features described at one week and represented attempts at tissue repair following surgery rather than a reaction to the silicon implant. Most sites showed areas of haemorrhage surrounded by loose granulation tissue, active proliferation of new blood vessels and a limited population of active fibroblasts. In a few cases these reparative features extended beyond the implantation site but, even in these cases, did not cause any major disruption to the surrounding tissue architecture.

By twelve weeks, the histological features represented a maturation of the granulation (repair) tissue response observed at four weeks. Although many of the implantation sites still showed significant infiltration by macrophages, lymphocytes and occasional fibroblasts, they showed no evidence of significant fibrotic scarring and a definite reduction in vascular proliferation. Furthermore, in no case did the persistent pathological changes extend beyond the implantation site.

In keeping with the observations made at the time of autopsy, histological examination of the major internal organs revealed no evidence of any pathology that could be ascribed to the silicon implants or any pre-existing disease in the experimental population. The major internal organs were also examined, with representative blocks being submitted for routine histopathological examination. Again, even at twelve weeks post-implantation, there were no features present indicative of either pre-existing disease or changes that could be ascribed to the implantation of the silicon or titanium materials.

The post-evaluation analysis of the scores for each implant type revealed a significantly higher level of chronic inflammation/fibrosis at weeks 4 and 12 for the porous silicon (uncoated) specimens when compared to the titanium controls (Table 2, Annex F). The nature of the tissue reaction noted is likely to be a reflection of the bioactive nature of the porous silicon implant type, suggesting that this material encourages tissue growth and interacts with biological systems. No other statistically significant differences were revealed for the other histological features or implant types at any of the time points.

The results of this study clearly demonstrate that there has been little or no reaction either the test or standard implant materials. The significant differences in histological features reflect changes which would be expected from any surgical procedure and are unrelated to the nature of the implant materials.

The significant differences in the chronic inflammation scores for the porous silicon at weeks 4 and 12 highlighted by the multivariant analysis are unlikely to be biologically significant in terms of biocompatability; to confirm this a further study involving comparison of porous silicon with titanium by subcutaneous implantation for 26 weeks has been performed and the results show no contra-indication against using porous silicon in an

implant or against using porous silicon as a resorbable carrier for micronutrients, microminerals or micro-payload drugs.

ANNEX A

SCORE GRADE CRITERIA

Acute Inflammatory Reaction.

Grade.	Description of Histological Features.
0.	No histological evidence of any acute inflammatory reaction.
1.	Small discrete clusters of inflammatory cells consisting predominantly of neutrophils and activated macrophages with occasional eosinophils and lymphocytes.
2.	Continuous sheets of acute inflammatory cells showing invasion of connective tissues in the immediate vicinity of the implanted material.
3.	Similar features to 2. above but associated with either necrosis of connective tissues and/or extension of cellular infiltrate beyond the vicinity of the implant.

Tissue Degeneration, Oedema, Haemorrhage and Necrosis.

Grade.	Description of Histological Features.
0.	No histological evidence of oedema, haemorrhage or tissue necrosis.
1.	Mild oedema of the connective tissues in the immediate vicinity of the implant.
2.	Significant oedema associated with either haemorrhage and/or necrosis in the vicinity of the implant.
3.	Similar features to 2. above but extending beyond the implant and involving adjacent connective tissues and muscle.

New Vessel and Granulation Tissue Formation.

Grade.	Description of Histological Features.
0.	No histological evidence of new vessel formation.
1.	Focal formation of isolated capillary loops in regions of tissue haemorrhage and/or necrosis.
2.	Continuous sheets of new vessel formation in association with local accumulations of fibroblasts to form loose granulation tissue limited to the vicinity of the implant.
3.	Similar features to 2. above but extending beyond the implant and involving adjacent connective tissues and muscle.

Persistent (Chronic) Inflammation and Tissue Fibrosis.

Grade.	Description of Histological Features.
0.	No histological evidence of either persistent (chronic) inflammation or early deposition of collagen (fibrosis).
1.	Small discrete foci of macrophages and lymphocytes which may or may not be associated with small populations of fibroblasts and new collagen deposition.
2.	Obvious sheets of chronic inflammatory cells and/or discrete granulomata associated with fibrous scar tissue in the vicinity of the implant.
3.	Similar features to 2. above but extending beyond the implant and involving adjacent connective tissues and muscle.

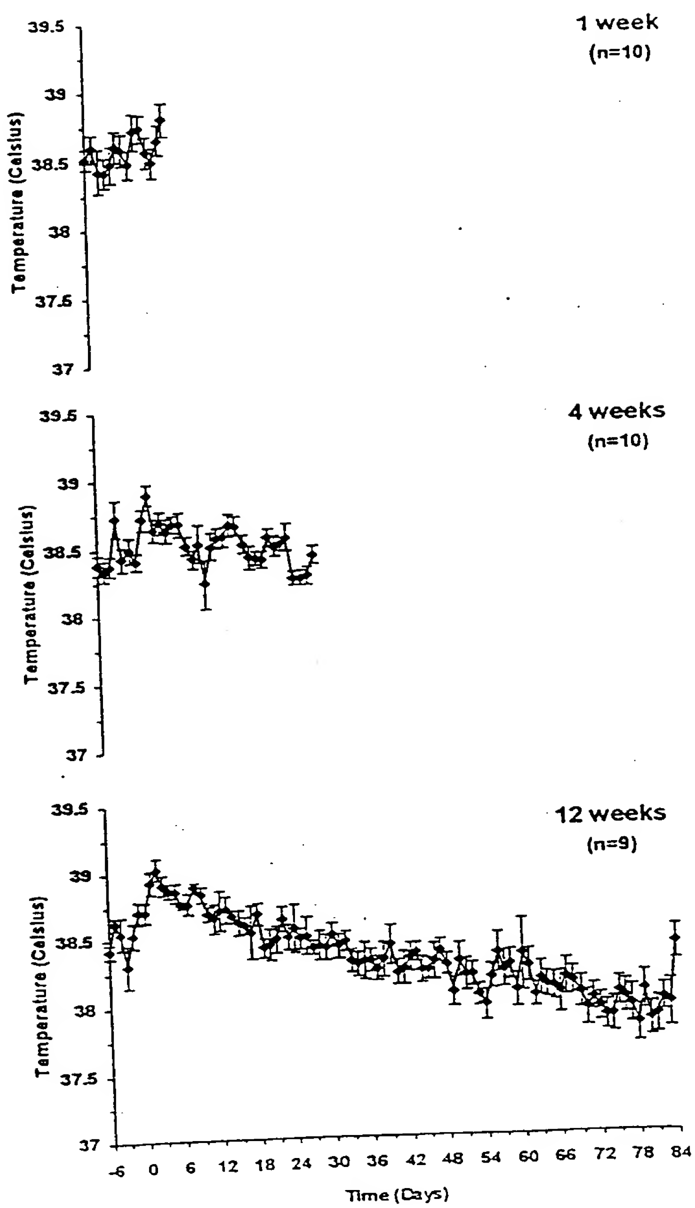

Figure 1. Mean (+/- sem) daily temperature for each of the three groups of guinea pigs.

Annex B

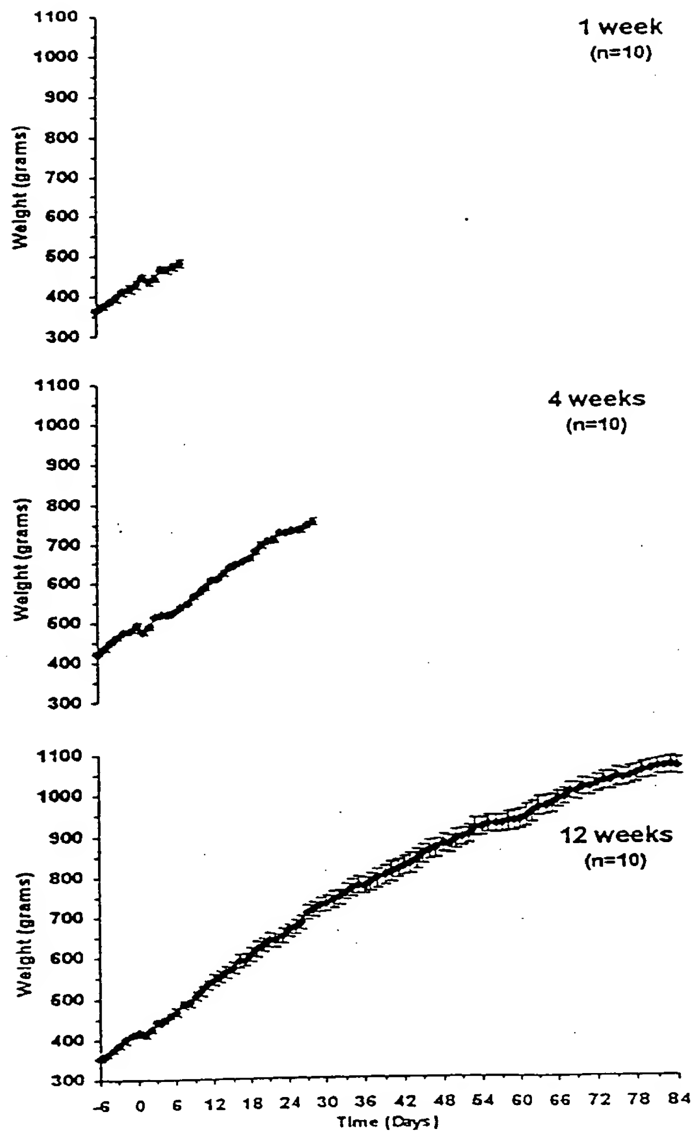

Figure 2. Mean (+/- sem) daily weight for each of the three groups of guinea pigs.

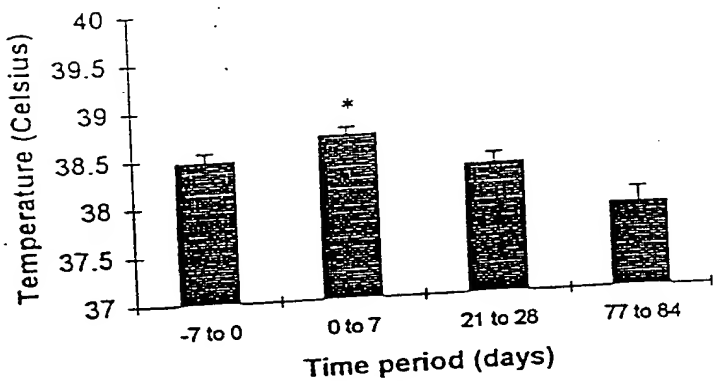

Figure 3. Comparison of guinea pig mean (+ sem) temperature for the 7 day control period prior to surgery (-7 to 0, n=30) with the 3 time periods prior to culling each group of animals (0 to7 days, n=30; 21 to 28 days, n=19[1]; 77 to 84, n=9[1]). *$p<0.05$ in comparison to control period.
[1] The temperature transponder of 1 animal malfunctioned; data for this animal is therefore missing.

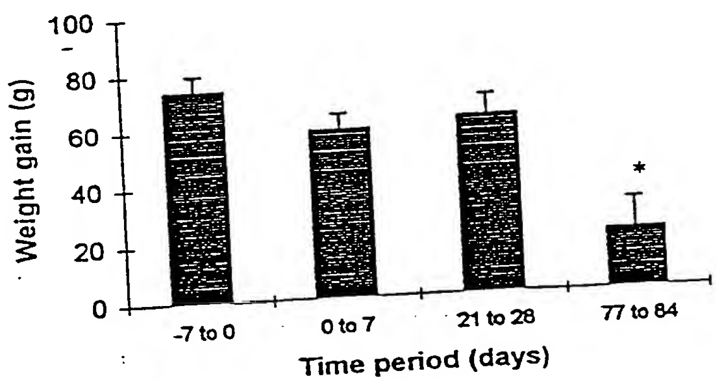

Figure 4. Comparison of guinea pig mean (+ sem) weight gain for the 7 day control period prior to surgery (-7 to 0, n=30) with the 3 time periods prior to culling each group of animals (0 to7 days, n=30; 21 to 28 days, n=20; 77 to 84, n=10). *$p<0.05$ in comparison to control period.

Annex C

PATHOLOGICAL SCORE GRADES PER ANIMAL FOR +1 WEEK TEST GROUP.

		Score Grade.															
		Inflammation				Tissue Degeneration/Necrosis.				New Vessels/Granulation Tissue.				Chronic Inflammation/Fibrosis.			
Group.	Animal No.	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI
+7 Days.	SI/GG/001.	1	1	1	2	0	0	0	1	1	1	1	2	0	0	0	0
+7 Days.	SI/GG/002.	2	1	1	1	1	0	0	0	2	1	1	1	0	0	0	0
+7 Days.	SI/GG/003.	1	1	1	0	0	1	0	0	1	2	1	1	0	0	0	0
+7 Days.	SI/GG/004.	1	1	2	1	0	0	1	0	1	1	2	1	0	0	0	0
+7 Days.	SI/GG/005.	1	2	2	2	0	1	1	1	1	2	2	1	0	0	0	0
+7 Days.	SI/GG/006.	1	1	2	1	0	0	1	0	1	1	1	1	0	0	0	0
+7 Days.	SI/GG/007.	1	1	1	1	0	0	0	0	1	1	1	2	0	0	0	0
+7 Days.	SI/GG/008.	1	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0
+7 Days.	SI/GG/009.	1	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0
+7 Days.	SI/GG/010.	1	1	1	1	0	0	0	0	2	1	1	1	0	0	0	0

TI Titanium control
BSI Bulk Silicon
PSI Porous Silicon
CoPSI Porous Silicon Coated with hydroxyapatite

Annex D

PATHOLOGICAL SCORE GRADES PER ANIMAL FOR +4 WEEK TEST GROUP.

		Score Grade.															
		Inflammation.				Tissue Degeneration/Necrosis.				New Vessels/Granulation Tissue.				Chronic Inflammation/Fibrosis.			
Group.	Animal No.	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI	TI	BSI	PSI	CoPSI
+4 Weeks.	SI/GG/011.	0	0	0	0	0	0	0	0	0	1	1	1	0	2	2	2
+4 Weeks.	SI/GG/012.	0	0	0	0	0	0	0	1	1	1	1	0	1	2	2	1
+4 Weeks.	SI/GG/013.	0	0	1	0	0	0	0	1	0	1	1	1	1	2	3	2
+4 Weeks.	SI/GG/014.	0	0	0	0	0	0	0	1	1	0	1	1	1	2	2	3
+4 Weeks.	SI/GG/015.	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1
+4 Weeks.	SI/GG/016.	0	0	1	0	0	0	1	0	1	1	2	1	2	2	3	2
+4 Weeks.	SI/GG/017.	0	0	0	0	0	0	1	0	1	1	1	1	2	2	2	1
+4 Weeks.	SI/GG/018.	0	0	0	0	0	1	0	1	1	1	0	1	2	1	2	1
+4 Weeks.	SI/GG/019.	0	0	0	0	0	0	0	1	1	1	1	0	1	2	1	1
+4 Weeks.	SI/GG/020.	0	0	0	0	0	0	0	0	0	1	1	0	0	1	2	1

TI Titanium control
BSI Bulk Silicon
PSI Porous Silicon
CoPSI Porous Silicon Coated with hydroxyapatite

Annex E

PATHOLOGICAL SCORE GRADES PER ANIMAL FOR +12 WEEK TEST GROUP.!

Group.	Animal No.	Inflammation. TI	Inflammation. BSI	Inflammation. PSI	Inflammation. CoPSI	Tissue Degeneration/Necrosis. TI	Tissue Degeneration/Necrosis. BSI	Tissue Degeneration/Necrosis. PSI	Tissue Degeneration/Necrosis. CoPSI	New Vessels/Granulation Tissue. TI	New Vessels/Granulation Tissue. BSI	New Vessels/Granulation Tissue. PSI	New Vessels/Granulation Tissue. CoPSI	Chronic Inflammation/Fibrosis. TI	Chronic Inflammation/Fibrosis. BSI	Chronic Inflammation/Fibrosis. PSI	Chronic Inflammation/Fibrosis. CoPSI
+ 12 Weeks.	SI/GG/021.	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0
+ 12 Weeks.	SI/GG/022.	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
+ 12 Weeks.	SI/GG/023.	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
+ 12 Weeks.	SI/GG/024.	0	0	0	0	0	0	1	0	0	0	1	0	0	0	2	0
+ 12 Weeks.	SI/GG/025.	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1
+ 12 Weeks.	SI/GG/026.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
+ 12 Weeks.	SI/GG/027.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
+ 12 Weeks.	SI/GG/028.	0	0	0	0	0	0	0	0	1	0	1	0	0	0	1	0
+ 12 Weeks.	SI/GG/029.	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2	2
+ 12 Weeks.	SI/GG/030.	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0

Score Grade.

TI Titanium control
BSI Bulk Silicon
PSI Porous Silicon
CoPSI Porous Silicon Coated with hydroxyapatite

Group	Inflammation		Tissue Degeneration/Necrosis		New vessels/Granulation Tissue		Chronic Inflammation/Fibrosis	
	Average rank	Significance	Average rank	Significance	Average rank	Significance	Average rank	Significance
Week 1	98.7		65.0		85.2		34	
Week 4	42.8		63.5		64.6		91.6	
Week 12	40.0		53.0		31.7		55.9	

Table 1. Average rank of scores for each histology category for each time period. A line between two rows in the significance column indicates a significant difference for those two groups ($p<0.05$; Kruskall-Wallis analysis).

		Average Rank			
Group	Implant Type	Inflammation	Tissue Degeneration	New Vessels/ Granulation	Chronic Inflammation/ Fibrosis
Week 1	Titanium	2.4	2.45	2.5	2.5
	BSI	2.4	2.45	2.5	2.5
	PSI	2.8	2.65	2.5	2.5
	CoPSI	2.4	2.45	2.5	2.5
Week 4	Titanium	2.4	2.1	2.15	1.85
	BSI	2.4	2.3	2.75	2.70
	PSI	2.8	2.5	2.75	3.20*
	CoPSI	2.4	3.1	2.35	2.25
Week 12	Titanium	2.5	2.45	2.35	2.15
	BSI	2.5	2.45	2.35	2.10
	Psi	2.5	2.65	2.95	3.30*
	CoPSI	2.5	2.45	2.35	2.45

Table 2. Average rank of scores for each implant type by histology category for each time period. * Denotes a significant difference between the rank for that implant type in comparison to the titanium control ($p<0.05$; Friedman analysis).

CLAIMS

1. A silicon implant having a beneficial substance associated with it, the implant being eroded when implanted in a mammalian body.

2. A silicon implant according to claim 1 in which the implant comprises porous silicon.

3. A silicon implant according to claim 1 which comprises polycrystalline silicon.

4. A silicon implant according to any preceding claim which is resorbed when implanted in a mammalian body.

5. A silicon implant according to any preceding claim which if left in the mammalian body for long enough is substantially completely resorbed.

6. A silicon implant according to any preceding claim in which said beneficial substance comprises an element of the periodic table.

7. A silicon implant according to claim 6 in which the element is a micromineral.

8. A silicon implant according to claim 7 in which the micromineral is from the group: selenium, manganese, molybdenum, chromium, vanadium, iodine, fluorine, cobalt (vitamin B12).

9. A silicon implant according to claim 6 in which the element is an essential trace element identified as such in Figure 5.

10. A silicon implant according to claim 6 in which the element is a therapeutic element.

11. A silicon implant according to claim 10 in which the element is from the group: lithium, gold, silver, platinum.

12. A silicon implant according to any preceding claim in which the substance is distributed through a volume of the material of said implant.

13. A silicon implant according to claim 11 in which the substance is distributed through substantially the whole volume of the material of the implant.

14. A silicon implant according to any preceding claim which comprises at least a region of porous silicon.

15. A silicon implant according to claim 14 which comprises substantially entirely porous silicon.

16. A silicon implant according to claim 14 or claim 15 which has a porosity of at least 3%, 4% or 5%.

17. A silicon implant according to any one of claims 14 to 15 which has a porosity of 30% or less.

18. A silicon implant according to any one of claims 14 to 16 which has a porosity in the range 3% to 10%, or in the range 10% to 60%.

19. A silicon implant according to any preceding claim in which there is provided a reservoir of beneficial substance, and a door leading to the

reservoir, the door being made of silicon material which is corroded in use so as to enable body fluid to contact the beneficial substance in the reservoir.

20. A silicon implant according to claim 19 in which there are a plurality of reservoirs.

21. A silicon implant according to claim 19 or claim 20 in which the reservoirs are adapted to expose or release their contents to body fluids sequentially with time.

22. A silicon implant according to any one of claims 19 to 21 in which there are a plurality of reservoirs, each having an associated door, and in which there are doors of different corrosion times, such that in use the reservoirs are breached at different times.

23. A silicon implant according to claim 22 in which there are doors of different thicknesses.

24. A silicon implant according to claim 22 in which there are doors which corrode at different rates.

25. A silicon implant according to any one of claims 19 to 24 in which there is an array of reservoirs.

26. A silicon implant according to any one of claims 19 to 25 in which the reservoirs comprise holes which contain the beneficial substance.

27. A silicon implant according to any one of claims 19 to 25 in which the reservoirs comprise regions of the implants which differentially

contain the beneficial substance to a significantly higher level than adjacent, non-reservoir, regions of the implant.

28. A silicon implant according to any one of claims 19 to 27 which comprises a first component defining in part a boundary of the or each reservoir and a second component defining in part a boundary of the or each reservoir.

29. A silicon implant according to claim 28 in which the two components are substantially the same.

30. A silicon implant according to any one of claims 19 to 29 in which there are at least of the order of ten, and preferably at least of the order of a hundred, reservoirs.

31. A silicon implant according to claim 30 in which there are at least or the order of a thousand reservoirs.

32. A silicon implant according to any one of claims 19 to 31 that has been micromachined.

33. An implant comprising a porous or polycrystalline carrier material that is corrode by mammalian subcutaneous physiological fluids, and a beneficial substance associated with the carrier material.

34. An implant according to claim 33 in which the carrier material is a semiconductor.

35. An implant according to claim 34 in which the carrier material is from the doped or undoped group: silicon, germanium, silicon carbide, silicon nitride.

36. An implant according to any one of claims 33 to 35 in which the implant comprises porous or polycrystalline semiconductor material.

37. An implant according to any one of claims 33 to 36 in which the beneficial substance comprises an element of the period table.

38. An implant according to claim 36 in which the element is a micromineral.

39. An implant according to claim 36 and any one of claims 1 to 35 in which instead of silicon another semiconductor material comprises the material that is eroded in use.

40. A silicon implant substantially as described herein with reference to Figures 4A to 4C and Figure 5 of the accompanying drawings.

41. A silicon implant substantially as described herein with reference to Figure 6, or Figure 7, or Figure 8, or Figure 9 of the accompanying drawings.

42. A method of making a silicon implant for the delivery of a beneficial substance to a subject, the method comprising taking a body of silicon, forming the silicon into an implantable implant, and introducing a beneficial substance into the silicon.

43. A method according to claim 42 which comprises applying a solution of micromineral to the silicon and migrating the micromineral into the silicon.

44. A method according to claim 42 or claim 43 comprising driving the beneficial substance into the silicon using heat.

45. A method according to any one of claims 42 to 44 comprising micromachining a hole or recess in the silicon.

46. A method according to claim 45 further comprising introducing said beneficial substance into the hole.

47. A method according to any one of claims 43 to 46 comprising applying a lid, or door, over the region which contains the beneficial substance to retain the beneficial substance.

48. A method according to any one of claims 45 to 47 comprising making a hole in a first component of silicon, making a complementary hole in a second piece of silicon, introducing said beneficial substance into one or both holes, and joining the two components together with their holes in register to define a closed reservoir which contains said beneficial substance.

49. A method according to any one of claims 45 to 48 comprising making a large number of holes in the implant, preferably simultaneously.

50. A method according to claim 49 which uses a photolithographic technique to make the holes.

51. A method according to any one of claims 42 to 50 comprising treating the body of silicon to make at least part of it porous.

52. A method according to claim 51 comprising making a body of silicon porous throughout substantially the whole of its volume.

53. A method according to any one of claims 42 to 50 comprising taking, or creating, a polycrystalline silicon body of material, or a layer or region of polycrystalline silicon.

54. A method of making a semiconductor implant for the delivery of a beneficial substance to a subject, the method comprising taking a body of semiconductor, forming the semiconductor into an implantable implant, and introducing a beneficial substance into the semiconductor.

55. A method according to claim 54 in which the semiconductor is from the group: silicon, germanium.

56. A method according to claim 54 or claim 55 comprising introducing a micromineral to the semiconductor.

57. A method according to any one of claims 54 to 56 and in accordance with any one of claims 42 to 53, in which the silicon material need not be silicon but could be another semiconductor.

58. A method of making a semiconductor implant substantially as described herein.

59. A method of making an implant for the delivery of beneficial substance to a subject, the method comprising treating a porous member of material that is erodable in vivo, creating an implant from the member, and introducing a beneficial substance into the implant.

60. An implant having a plurality of reservoirs, a plurality of beneficial substance charges provided in said reservoirs, and a plurality of barrier regions, or doors, provided adjacent said reservoirs, the doors having a plurality of different erosion times when implanted, the arrangement being such that in use the doors are broken down sequentially in order to stagger the release of the contents of the reservoirs.

61. An implant according to claim 60 in which the doors comprise a semiconductor material.

62. An implant according to claim 60 or claim 61 in which substantially the entire implant comprises semiconductor material.

63. An implant according to claim 62 in which the implant comprises the same semiconductor material throughout.

64. An implant according to any one of claims 60 to 63 in which there are at least five reservoirs.

65. An implant according to claim 64 in which there are at least ten reservoirs.

66. An implant according to claim 64 in which there are at least fifty reservoirs.

67. An implant according to claim 64 in which there are at least one hundred reservoirs.

68. An implant according to claim 64 in which there are at least of the order of hundreds of reservoirs.

69. A method of delivering a beneficial substance to a subject comprising implanting an implant into the subject and arranging for different regions of the implant to be eroded through or away at different times by arranging for said regions to require different exposure times to the corroding fluids experienced in use to be breached, and using the sequential breaching of said different regions to release sequentially different reservoirs of beneficial substance that were retained in or behind said different regions of the implant.

70. The use of corrodable or resorbable silicon, or other semiconductor material, in the preparation of an implant for the delivery of a physiologically active substance to a subject.

71. The use of the corrosion or resorbtion of silicon or other semiconductor material in an implant in order to release a substance entrained in the material of the silicon or semiconductor, or to open a door to a reservoir of the substance.

ABSTRACT

IMPLANTS FOR ADMINISTERING SUBSTANCES AND METHODS OF PRODUCING IMPLANTS

A porous silicon implant (42;60) impregnated with a beneficial substance, such as a micromineral required for healthy physiology, is implanted subcutaneously and is entirely corroded away over the following months/year to release the micromineral in a controlled manner. In a second embodiment the implant (62) may have a large number of holes (72) which contain beneficial substance and which are closed by bio-errodable doors (76,78) of different thickness so as to stagger the release of the beneficial substance over time as the doors are breached.

It is recommended that Figure 6 accompany the abstract when published.

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FIG. 1A

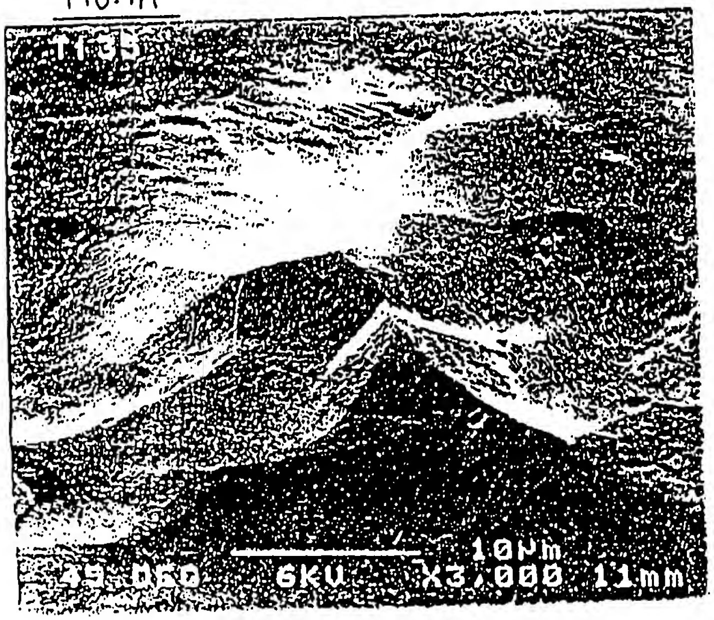


FIG 1B

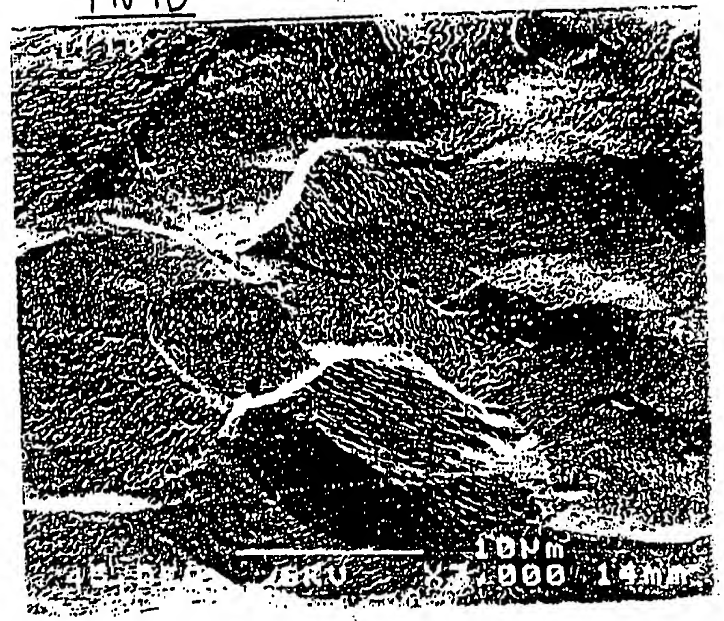


FIG 1C

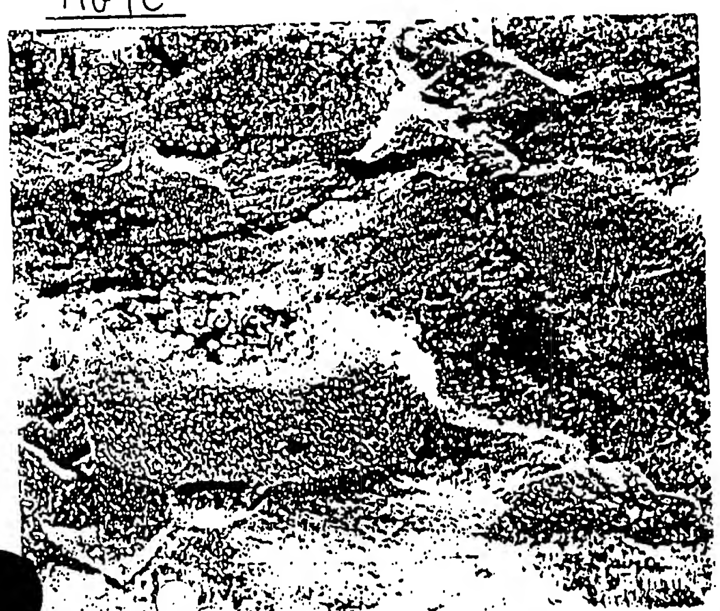
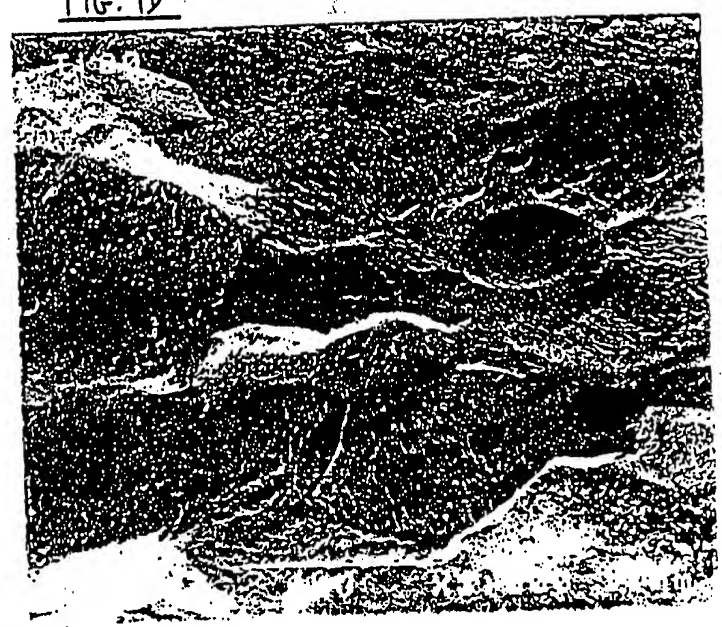


FIG. 1D



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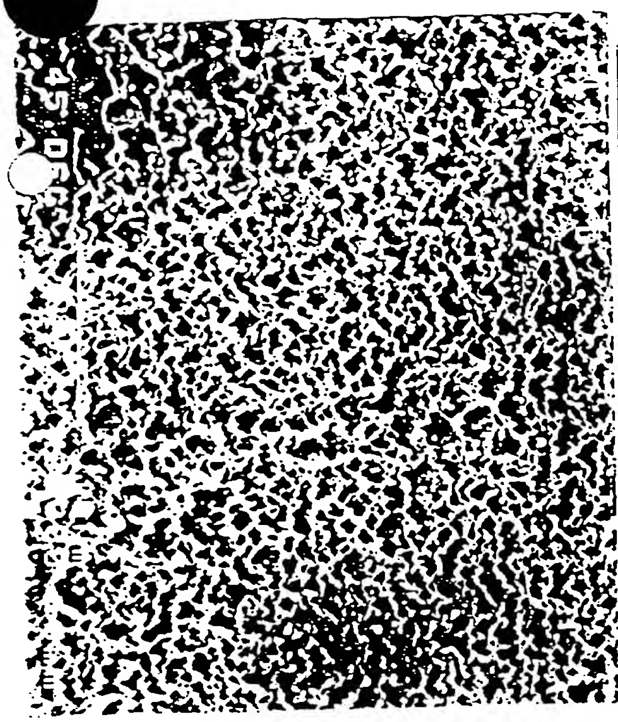

FIG. 2C

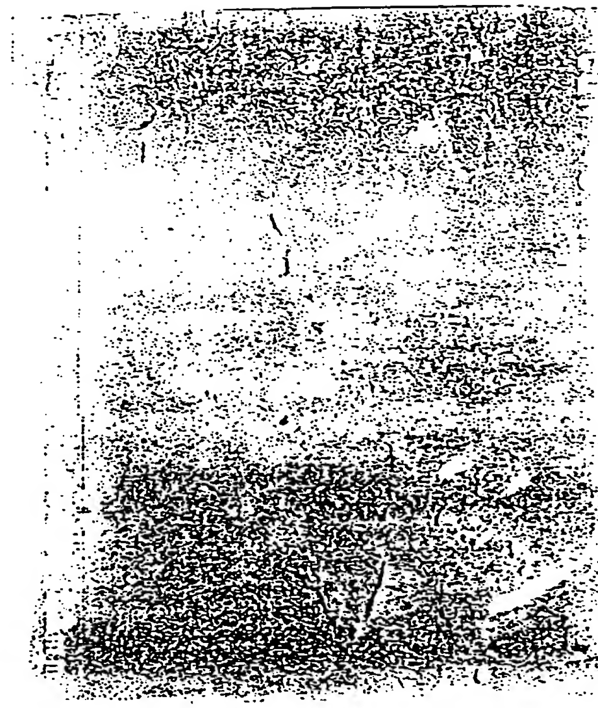

FIG 2A

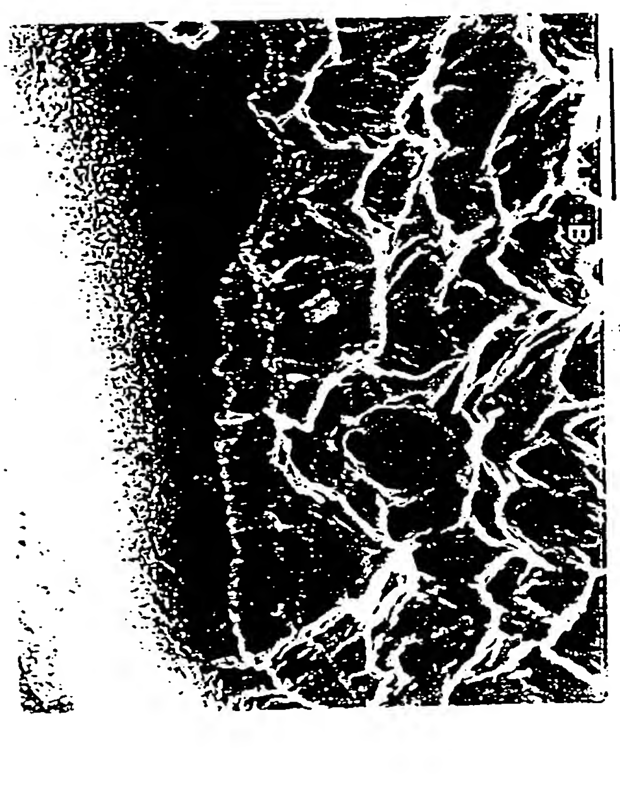

FIG 2D

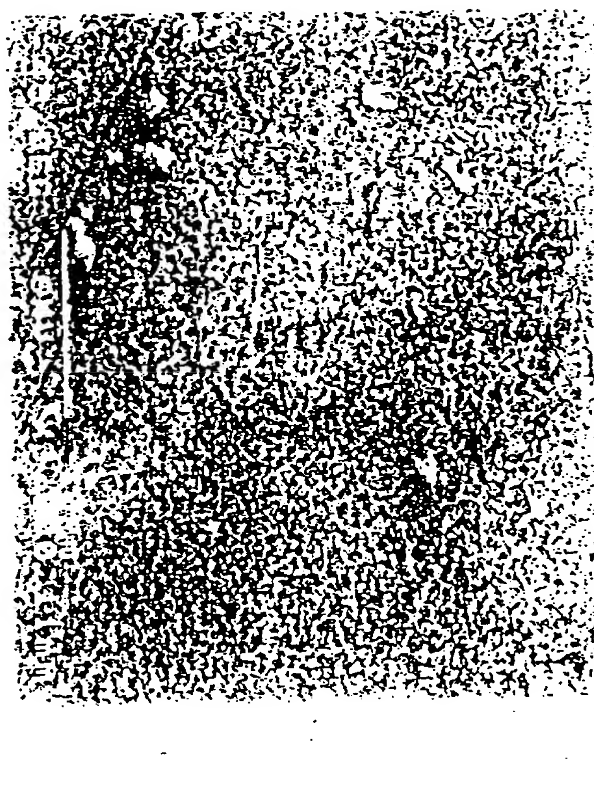

FIG 2B

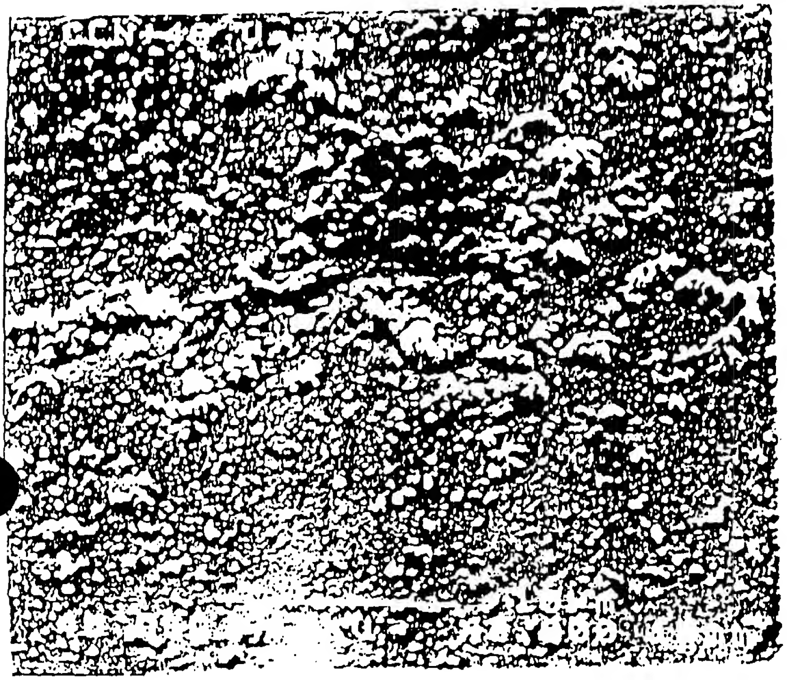

FIG. 3A

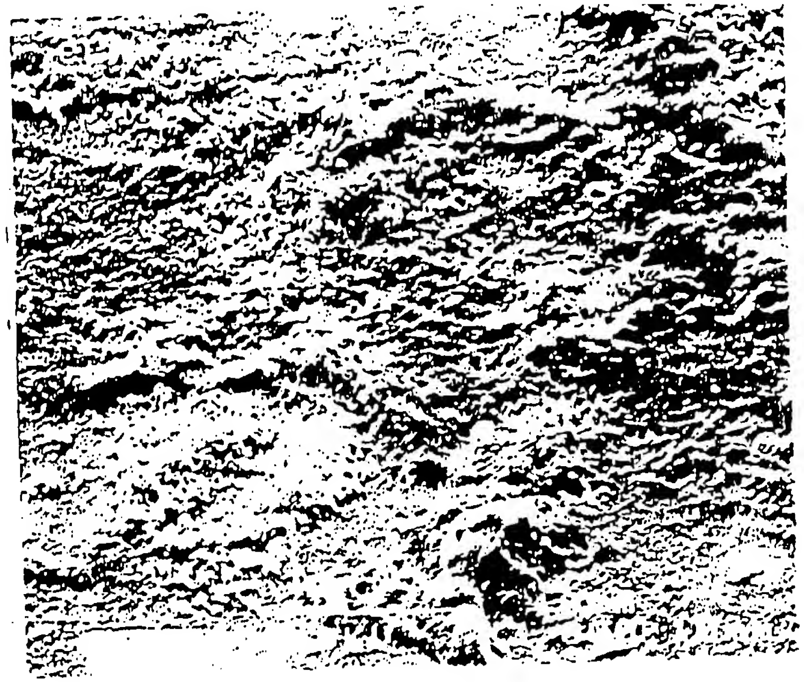

FIG. 3B

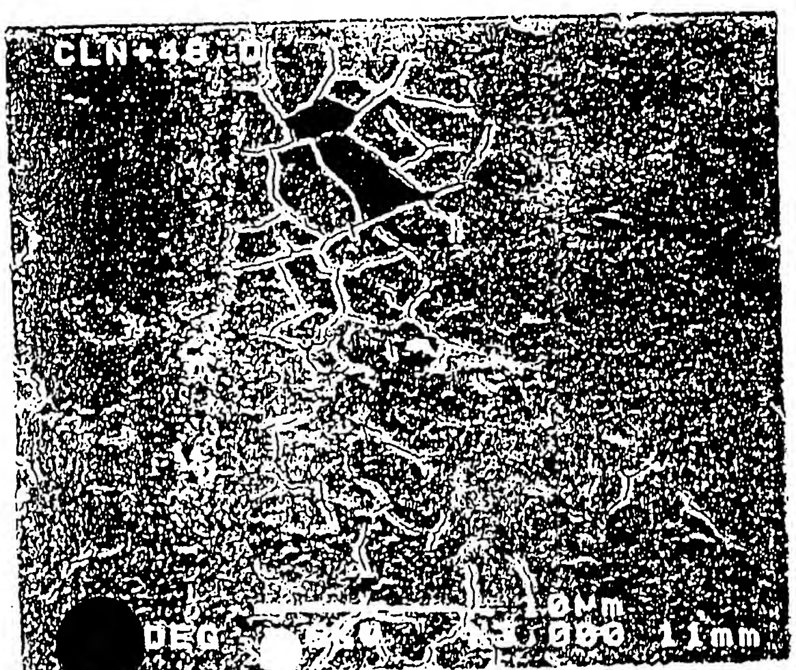

FIG. 3C

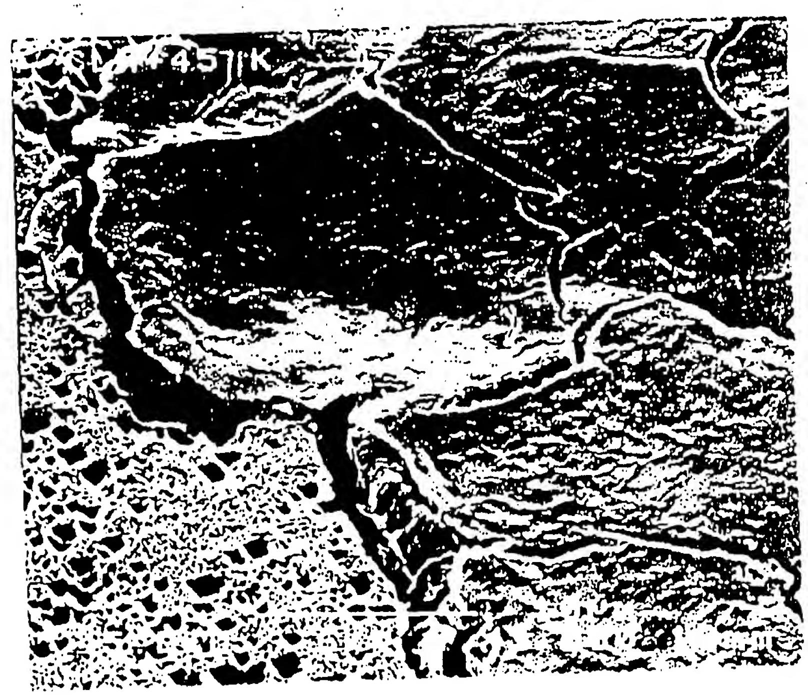

FIG. 3D

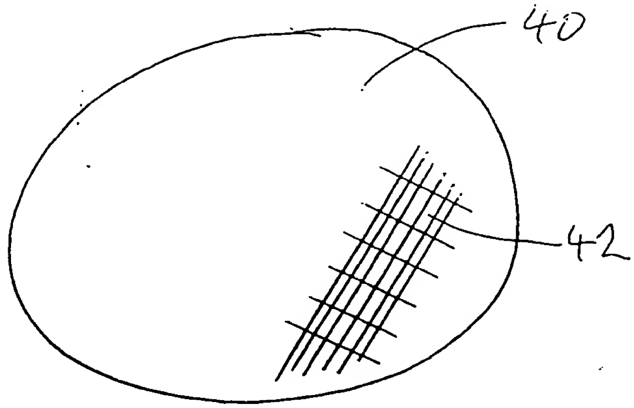

FIG 4A

FIG. 4B

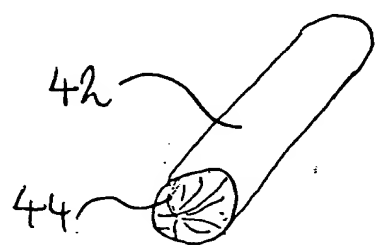

FIG. 4C

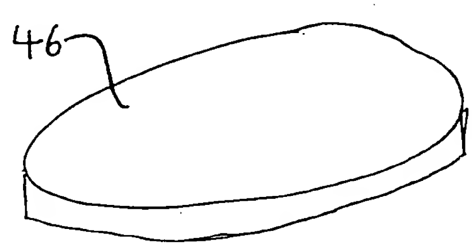

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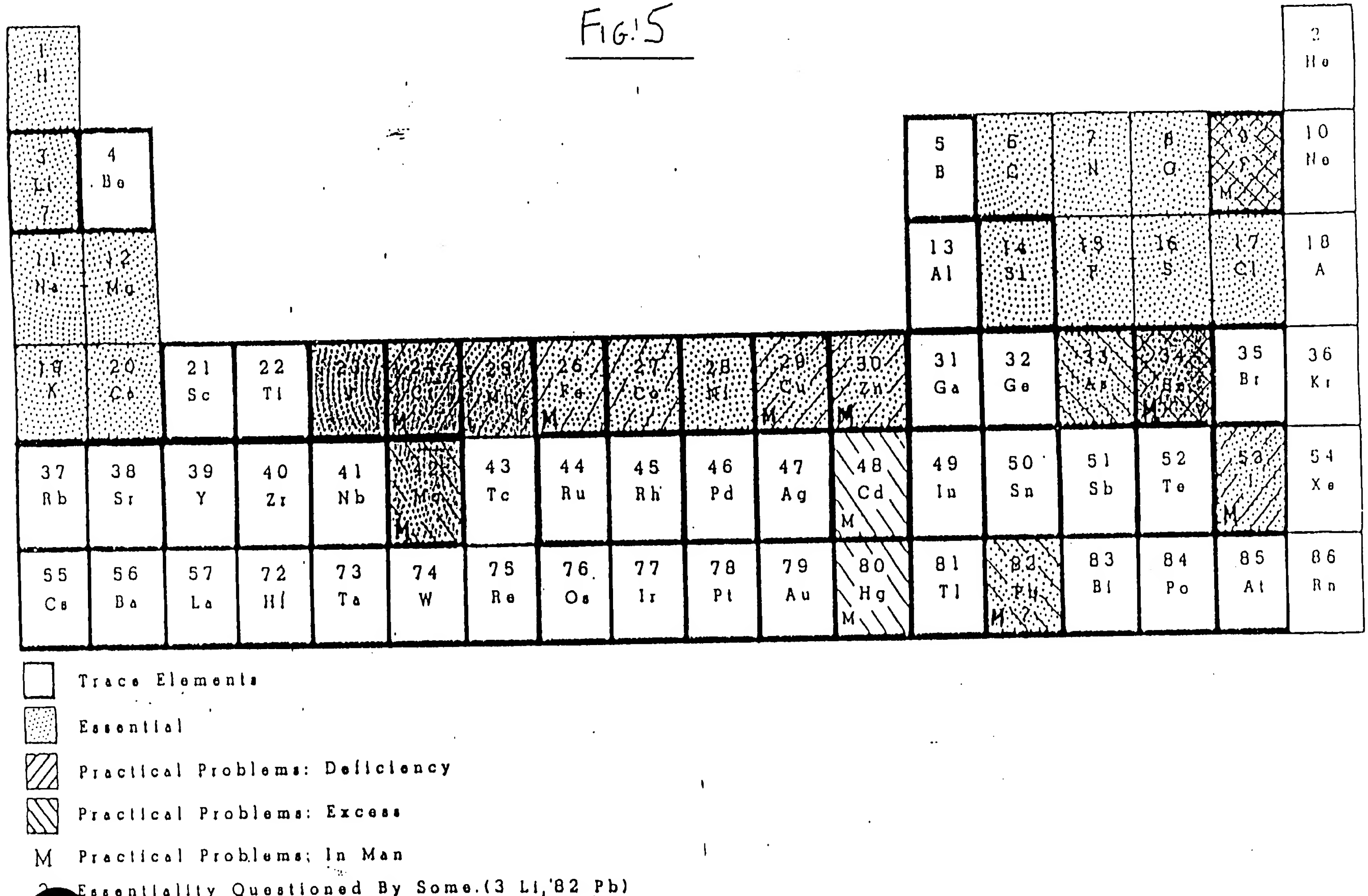
FIG. 5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3 Li ?
4 Be
5 B
6 C
7 N
8 O
9 F M
10 Ne
11 Na
12 Mg
13 Al
14 Si
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17 Cl
18 A
19 K
20 Ca
21 Sc
22 Ti
26 Fe M
27 Co
28 Ni
29 Cu M
30 Zn M
31 Ga
32 Ge
33 As
34 Se M
35 Br
36 Kr
37 Rb
38 Sr
39 Y
40 Zr
41 Nb
42 Mo M
43 Tc
44 Ru
45 Rh
46 Pd
47 Ag
48 Cd M
49 In
50 Sn
51 Sb
52 Te
53 I M
54 Xe
55 Cs
56 Ba
57 La
72 Hf
73 Ta
74 W
75 Re
76 Os
77 Ir
78 Pt
79 Au
80 Hg M
81 Tl
82 Pb M ?
83 Bi
84 Po
85 At
86 Rn
Trace Elements
Essential
Practical Problems: Deficiency
Practical Problems: Excess
M Practical Problems: In Man
? Essentiality Questioned By Some.(3 Li,'82 Pb)

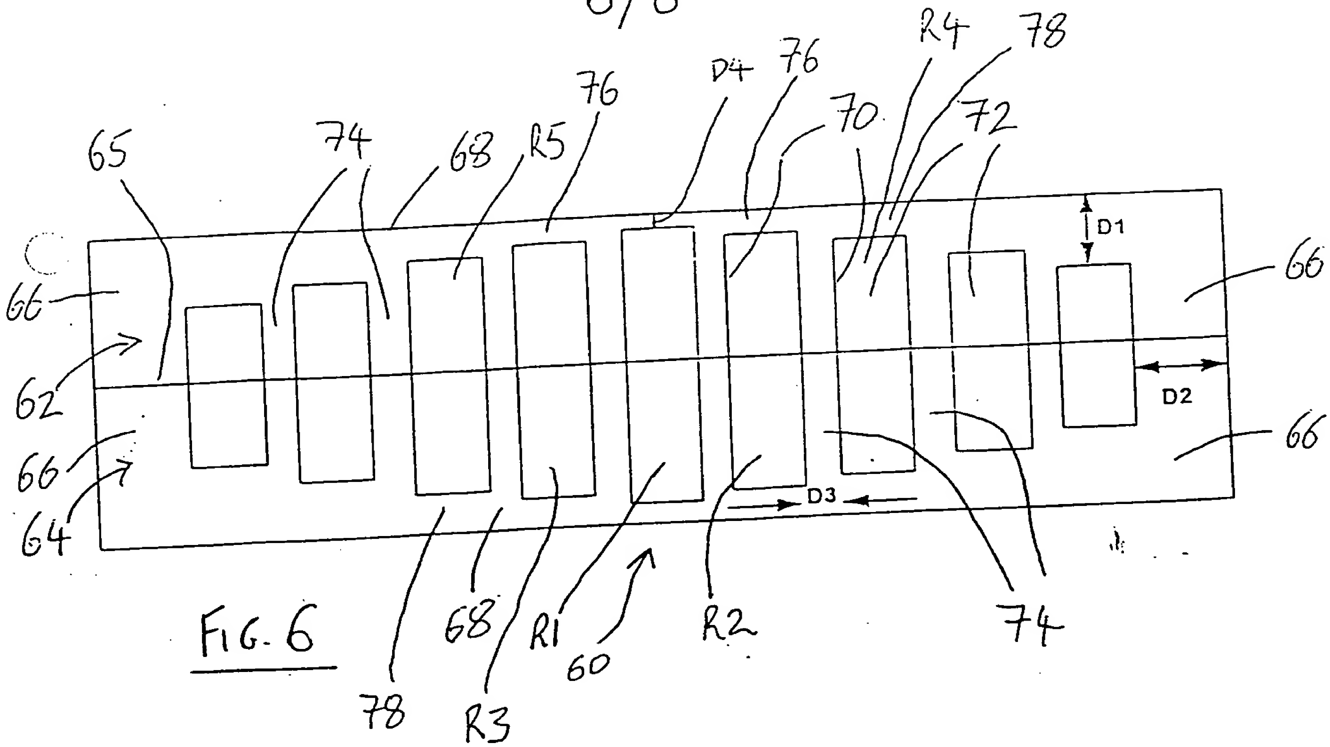

FIG. 6

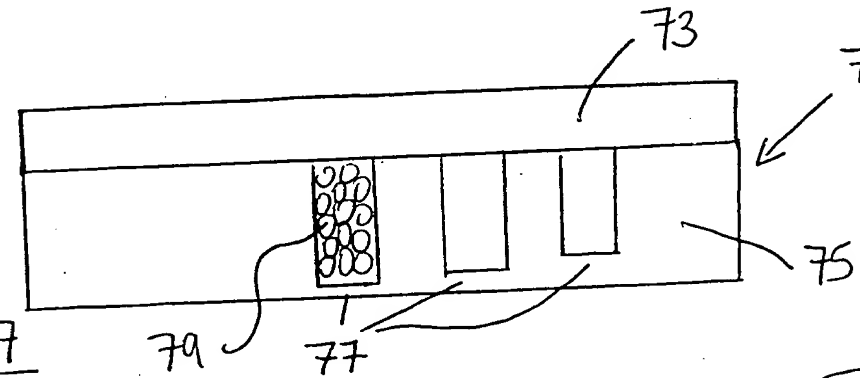

FIG7

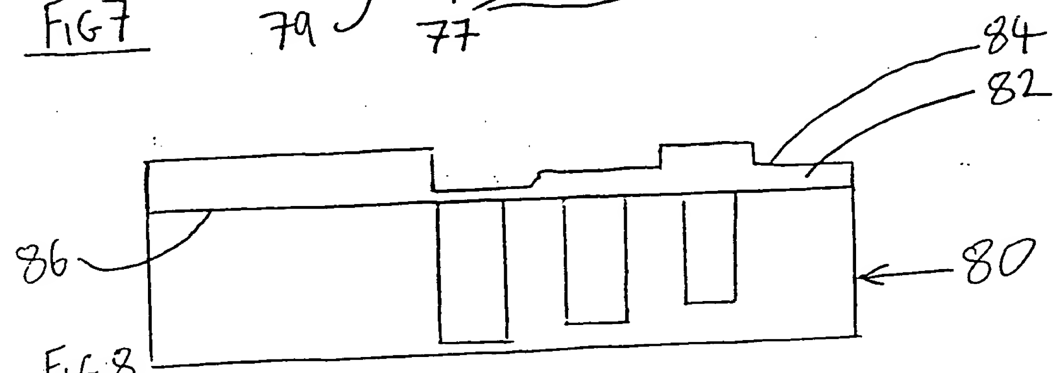

FIG.8

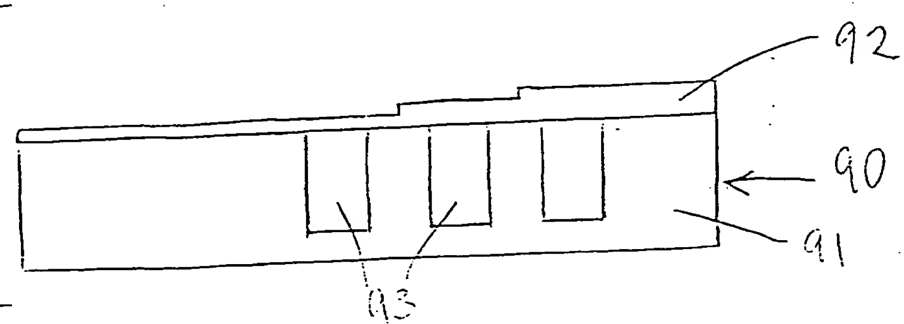

FIG.9

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Barker Brettell

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